Potential Developmental Susceptibility to Tetrachloroethylene (Perc)

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Abstract:

The US EPA is currently preparing a chemical assessment of the health effects of tetrachloroethylene (perc), a solvent widely used in dry cleaning, textile processing, and metal-cleaning operations. The limited data available for childhood and early-life stages represent a period of potential susceptibility based upon exposure and developmental outcomes. Human epidemiological and experimental animal studies suggest a number of potential adverse health effects at various stages of development, although the evidence is not yet definitive. Due to perc's high volatility and lipid solubility, exposure scenarios of concern include placental transfer, inhalation near points of use (particularly indoors), and consumption of contaminated water or breast milk. During preconception, there is some evidence that perc exposure results in subtle non-adverse effects on human sperm, which is consistent with findings of abnormal sperm in mice exposed to perc. Findings of spontaneous abortion and reduced birth weight in humans are supported by several rodent studies, while limited findings of congenital anomalies and intrauterine growth restriction in both animal and human studies are not conclusive. There is some evidence of visual impairment in children with exposure to perc from dry cleaning establishments and in children of mothers exposed to organic solvents, including perc. Furthermore, there is limited evidence of motor and cognitive deficits in children whose mothers were prenatally exposed to organic solvents, some of whom were employed as dry cleaners. For all human data, a key limitation is a lack of statistical power and dose–response information. To better characterize early childhood risk from exposure to perc, more research is needed.

Conclusions:

- Non-cancer outcomes of concern in early life stages from available studies are:
  - Neurological impairment
  - Spontaneous abortion
  - Mortality
- There are various sources of uncertainty, including:
  - Limited exposure assessment for non-occupational sources
  - Limited dose-response characterization
  - Limited statistical power for neurobehavioral data, small for gestational age, and mortality.

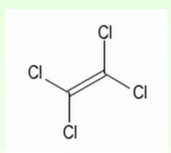
Future Research Needs:

(1) Improved exposure assessment, including:
- Better characterization of exposure pathways, with particular attention to exposure during critical periods of development and child-specific behaviors (e.g., dairy ingestion)
- Better characterization of exposure pathways resulting in aggregate risks
- Increased utilization of biomarker data (e.g., tissue concentration, exhaled breath, urinary metabolites).

(2) Improved hazard characterization, including:
- Child-specific toxicokinetics (e.g., placental and dermal absorption, organ distribution, metabolic capacity)
- Improved methodology to evaluate subtle neurological effects in children in an age-appropriate manner
- Additional studies characterizing immunotoxic response
- Better characterization of mode of action (MOA)
- Longitudinal studies to capture persistent and latent effects.

(3) Validation of physiologically-based pharmacokinetic models incorporating child-specific (blood flow, organ and body weight, etc.) and maternal-specific parameters (e.g., maternal inhalation exposure and resulting concentration in breast milk).

Outcome	Effect Seen		No Effect Seen	
Preconception	**Human**	**Experimental Animal**	**Human**	**Experimental Animal**
Decreased fertility, decreased litter size	(o) Eskenazi et al., 1991a (o) Eskenazi et al., 1991b (o) Rachootin & Olsen, 1983 (o) Sallmén et al., 1995	(ih) guinea pig: Kyrklund & Haglid, 1991 (ih) rat: Berger & Horner, 2003 (ig) rat: Narotsky & Kavlock, 1995 (ih) rat: Tinston, 1994	(w) Lagakos et al., 1986	
Abnormal sperm	(o) Eskenazi et al., 1991b	(ih) mouse: Beliles et al., 1980		(ih) rat: Beliles et al., 1980
Hormonal disturbances	(o) Rachootin & Olsen, 1983			
Prenatal	**Human**	**Experimental Animal**	**Human**	**Experimental Animal**
Increased embryo toxicity		(c) rat: Saillenfait et al., 1995		
Increased maternal toxicity		(ih) mouse: Schwetz et al., 1975 (ig) rat: Narotsky & Kavlock, 1995 (ih) rat: Schwetz et al., 1975		
Decreased maternal weight gain		(ig) rat: Narotsky & Kavlock, 1995 (ih) rat: Tinston, 1994		(ih) rabbit: Hardin et al., 1981 (ih) rat: Hardin et al., 1981
Increased spontaneous abortion, fetal loss/ resorption	(o) Ahlborg et al., 1990 (o) Bosco et al., 1987 (o) Doyle et al., 1997 (o) Kyyrönen et al., 1989 (o) Lindbohm et al., 1990 (o) Olsen et al., 1990 (o) Windham et al., 1991	(ig) rat: Narotsky & Kavlock, 1995 (ih) rat: Schwetz et al., 1975	(o) Eskenazi et al., 1991a (o) McDonald et al., 1986 (o) McDonald et al., 1987 (w) Lagakos et al., 1986 (o) Taskinen et al., 1989	(ih) rabbit: Hardin et al., 1981 (ih) rat: Hardin et al., 1981
Birth	**Human**	**Experimental Animal**	**Human**	**Experimental Animal**
Difficult labor		(ih) rat: Tinston, 1994		
Perinatal death	(w) Lagakos et al., 1986 (w) Shawn and Robins, 1986	(ig) rat: Narotsky & Kavlock, 1995 (ih) rat: Tinston, 1994	(w) Lagakos et al., 1986	
Stillbirth		(ih) rat: Tinston, 1994	(o) Kyyrönen et al., 1989 (o) Olsen et al., 1990 (o) Taskinen et al., 1989 (o) Windham et al., 1991	
Birth defects – neurological	(w) Bove et al., 1992 (w) Bove et al., 1995 (w) Lagakos et al., 1986		(w) Bove et al., 1992 (w) Bove et al., 1995 (o) Kyyrönen et al., 1989 (o) Olsen et al., 1990 (o) Taskinen et al., 1989 (o) Windham et al., 1991	
Birth defects – muscular or skeletal	(w) Lagakos et al., 1986	(ih) mouse: Schwetz et al., 1975 (ig) rat: Narotsky & Kavlock, 1995	(w) Lagakos et al., 1986 (o) Kyyrönen et al., 1989 (o) Olsen et al., 1990 (o) Taskinen et al., 1989 (o) Windham et al., 1991	(ih) rabbit: Hardin et al., 1981 (ih) rat: Hardin et al., 1981 (ih) rat: Nelson et al., 1980
Decreased birth weight, IUGR, SGA	(w) ATSDR, 1998 (w) Sonnenfeld et al., 2001 (o) Windham et al., 1991	(ih) guinea pig: Kyrklund & Haglid, 1991 (ih) mouse: Schwetz et al., 1975 (ig) rat: Narotsky & Kavlock, 1995 (ih) rat: Nelson et al., 1980 (ih) rat: Tinston, 1994	(w) Bove et al., 1992 (w) Bove et al., 1995 (o) Kyyrönen et al., 1989 (o) Olsen et al., 1990 (o) Taskinen et al., 1989 (o) Windham et al., 1991	(ih) rabbit: Hardin et al., 1981 (ih) rat: Hardin et al., 1981
Postnatal	**Human**	**Experimental Animal**	**Human**	**Experimental Animal**
Decreased weight gain		(ig) rat: Chen et al., 2002 (ih) rat: Nelson et al., 1980 (ih) rat: Tinston, 1994		
Decreased testes weight		(ih) rat: Tinston, 1994		
Altered brain biochemical markers		(ih) guinea pig: Kyrklund & Haglid, 1991 (ih) rat: Nelson et al., 1980		
Leukemia	(w) MA DPH, 1997			
CNS/behavioral effects	(o) Till et al., 2001a	(ip) mouse: Umezu et al., 1997 (ig) rat: Chen et al., 2002 (ih) rat: Nelson et al., 1980 (ih) rat: Tinston, 1994		
Effects on locomotion, reflex, balance		(ig) mouse: Fredriksson et al., 1993 (ip) mouse: Umezu et al., 1997 (ig) rat: Chen et al., 2002 (ip) rat: Motohashi et al., 1993 (ih) rat: Nelson et al., 1980 (ih) rat: Tinston, 1994		
Visual impairment	(ih) NYDOH, 2005 (ih) Schreiber et al., 2002 (o) Till et al., 2001b (o) Till et al., 2004 (ih) Till et al., 2005			
Asthma	(ih) Delfino et al., 2003a		(ih) Delfino et al., 2003b	
Seizure susceptibility threshold		(ig) rat: Chen et al., 2002		
Change in pain threshold		(ig) rat: Chen et al., 2002		
Coma, Death	(ih) Garnier et al., 1996 (ig) Koppel et al., 1995			



KEY:
c = in vitro cell culture
ig = direct ingestion exposure, gavage
ih = inhalation exposure
ip = intraperitoneal
o = occupational exposure (likely inhalation, possibly dermal)
r = residential exposure (likely inhalation, possibly water ingestion or dermal)
w = water ingestion

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